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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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Kathleen M Williams Esq
Banner & Witcoff LTD
28 State Street 28th Floor
Boston MA 02109

EXAMINER	
LEFFERS JR,G	

ART UNIT	PAPER NUMBER
1636	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/492,590	CARTENS, CARSTEN-PETER	
	Examiner	Art Unit	
	Gerald Leffers	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Receipt is acknowledged of applicant's amendment, filed 2/9/01 as Paper No. 11, in which claims 20 and 35 were amended, and in which claim 17 was canceled without prejudice. Receipt is also acknowledged of an accompanying Rule 132 declaration by Mary Buchanan, Director of Product Management for Stratagene, concerning the commercial success of various embodiments of the claimed invention.

Any rejection from the previous office actions not addressed in this action has been withdrawn. Because new rejections are made in this action which were not necessitated by applicant's amendment, this action is not final.

Claims 1-16 and 18-44 are pending in this application.

Specification

The disclosure is objected to because of the following problem: the specification refers to Tables 1-4 at various points (e.g. page 11, line 6). There are no tables present in the application papers. There is no indication that Tables 1-4 were ever filed in the transmittal papers. Deletion of any reference to these tables may necessarily constitute NEW MATTER. Also, these tables, apparently specifying codon usage frequencies in different cell types, are essential matter for practicing applicant's invention. It is noted that although tables are presented in provisional application 60/117,355, the benefit of which is claimed by the instant specification, there is no incorporation by reference of the provisional application made in the instant specification or

transmittal papers. Therefore, incorporation of the tables present in the provisional application into the instant application would constitute NEW MATTER.

The disclosure is objected to because of the following informalities: there is no description of Figure 2 in the Brief Description of the Drawings and the description of the following figures appear to be misnumbered. Also, references to the figures made in the specification (e.g. in the working examples) appear to be consistently drawn to the wrong figure.

Appropriate correction is required.

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(1). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 18-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection.**

The claimed invention is drawn towards a host cell/vector system for the expression of polypeptides whose genes comprise codons which are rarely used in the host cell of the expression system. The host cells and/or vectors of the system comprise and array of tRNA genes corresponding to the rarely used codons present in the gene encoding the desired protein. Thus, the crux of the system is the combination of rarely used codons for a particular host cell with corresponding tRNA genes and genes comprising codons rarely used in that particular host cell. The claimed invention literally encompasses a combination of any gene coding sequence comprising codons which might be rarely used in a host cell, any host cell derived from any source and any tRNA gene encoding a tRNA corresponding to a rarely used codon. Thus, the claims are very broad genus claims with regard to the combination of host cell type, gene comprising rarely used codons for that cell type and tRNA genes corresponding to the rarely used codons for that host cell type.

It is known in the art that codon usage varies among different types of host cells. Thus, one of skill in the art would not expect the same rare codon usage to be present in cells of different origin and would not expect that a description of host cells/rarely used codons/corresponding tRNA genes for one cell type to be descriptive of the structural/functional characteristics of the analogous system for all other cell types. While the specification provides a broad list of proposed cell types for practicing the claimed invention (e.g. various plant and

animal cell types, various fungal cell types, etc.), the actual description and relevant working examples provided in the specification for combinations of rarely used codons/host cell type/tRNA genes are limited to expression of polypeptides in E.coli. Examples are provided wherein rarely used codons in E.coli are compensated for by the presence of genes encoding tRNAs corresponding to the rarely used codons. While the specification refers to Tables 1-4 which purportedly refer to frequencies of codon usage in different cell types, there are no tables present in the application as filed. No such codon frequency data are provided in the specification other than for E.coli. Moreover, no tRNA genes corresponding to such rarely used codons for other cell types are provided in the specification. The tRNA genes described in the specification (argU, leuW, ileX, ileY, proL) are all described in the context of expression of a protein in E.coli. The prior art does not appear to provide an obvious description of what such a system would look like in other cell types as the prior art deals primarily with the expression of desired eukaryotic polypeptides in E.coli. In the absence of any significant description or relevant example in the specification or prior art for embodiments of the claimed invention other than for E.coli cells wherein the rarely used codons correspond to the tRNA genes argU, leuW, ileX, ileY and proL, one of skill in the art would not be able to envision a representative number of embodiments of the claimed genus. Therefore, one of skill in the art would reasonably conclude applicant was not in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-10, 15-16, 19, 22-27, 32-40, 42-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Zdanovsky (U.S. Patent No. 6,214,602; see the entire document). **This is a new rejection.**

Applicant claims a series of host cells, vectors and methods for production of a protein of interest wherein the protein of interest comprises rarely used codons and wherein the claimed vector comprises two or three genes encoding tRNAs specific for the rare codons found within the protein of interest. The host cell and/or vector can comprise an array of three or more rare tRNA genes, which can specifically include combinations of argU, ileY, proL, leuW and tRNA genes specific for rarely used glycine codons. Expression of the tRNA genes can be under control of the T7 RNA polymerase-specific promoter. The host cell can be a bacterial cell. The host cell can be protease deficient (e.g. Lon- and OmpT-), Rec+ and/or EndA1 deficient. In embodiments wherein the vector comprises two tRNA genes corresponding to rarely used codons, the tRNA genes do not consist of argU and ileX.

The Zdanovsky patent (i.e. the '602 patent) discloses vectors and methods for the overproduction of Clostridium toxins and proteins by hosts such as E.coli. The methods feature the use of host cells containing a recombinant expression vector, wherein the expression vector encodes tRNAs that recognize rare codons and wherein the host cell expresses at least a fragment of at least one clostridial protein. The rare codons, in preferred embodiments, are selected from the group consisting of ATA, AGA, CTA, AUA, AGA and CUA. The '602 patent claims and teaches a series of constructs which comprise rarely used tRNA genes (e.g. see Figure 2, Examples 1 and 2, claims). For example, the vector pACYC-IRL10 comprises the genes ileX, argU and leuW under control of the T7 RNA polymerase promoter. The vector pACYC-RL5 comprises the argU and leuW genes under control of the T7 RNA polymerase promoter. Each of the claimed recombinant vectors is utilized in a series of experiments (see examples 1 and 2) to express in E.coli (i.e. BL21(DE3) different clostridial proteins which were then purified by SDS-PAGE (see Examples 2 and 3, Figures 3-6). The E.coli strain BL21(DE3) is lon^-, $ompT^-$ and $RecA^+$, and also features the IPTG-inducible expression of the T7 RNA polymerase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zdanovsky (U.S. Patent No. 6,214,602, April 10, 2001; see the entire document) in view of Wnendt (X; Biotechniques, Vol. 17, No. 2, pages 270-272; see the entire document). **This is a new rejection.**

The Zdanovsky patent (i.e. the '602 patent) discloses vectors and methods for the overproduction of Clostridium toxins and proteins by hosts such as E.coli (Abstract). The methods feature the use of host cells containing a recombinant expression vector, wherein the expression vector encodes tRNAs that recognize rare codons and wherein the host cell expresses at least a fragment of at least one clostridial protein. The rare codons, in preferred embodiments, are selected from the group consisting of ATA, AGA, CTA, AUA, AGA and CUA. The '602 patent claims and teaches a series of constructs which comprise rarely used tRNA genes (e.g. see Figure 2, Examples 1 and 2, claims). For example, the vector pACYC-IRL10 comprises the genes ileX, argU and leuW under control of the T7 RNA polymerase promoter. The vector pACYC-RL5 comprises the argU and leuW genes under control of the T7 RNA polymerase promoter. Each of the claimed recombinant vectors is utilized in a series of experiments (see examples 1 and 2) to express in E.coli (i.e. BL21(DE3) different clostridial proteins which were then purified by SDS-PAGE (see Examples 2 and 3, Figures 3-6). The E.coli strain BL21(DE3) is lon^-, $ompT^-$ and $RecA^+$, and also features the IPTG-inducible expression of the T7 RNA polymerase.

The Zdanovsky patent does not teach the use of $endA^-$ E.coli strains.

Wnendt teaches that the use of endA$^-$ strains allows for great and higher quality yields of plasmid DNAs from bacterial cells (page 270, column 1, paragraph 1).

It would have been obvious to one of ordinary skill in the art to introduce an endA mutation into the strain of E.coli used as a host cell in the vector/host systems made from the teachings of the '602 patent to express heterologous polypeptides whose genes comprise different rarely-used codons because Wnendt teaches that the lack of EndA nuclease activity results in higher quantity and quality of plasmids isolated from E.coli strains bearing an endA mutation. One would have been motivated to do so in order to increase the yield and quality of plasmids recovered from the host cells during cloning of the vectors comprising the tRNA genes corresponding to the rarely used codons present in the gene encoding a desired polypeptide. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing an endA$^-$ strain of E.coli in the methods made from the combined teachings above for expression of a gene encoding a desired polypeptide comprising rarely used codons.

Claims 1-5, 10-16, 22-23 and 26-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U) in view of Makoff et al (V). **This rejection is maintained for reasons of record in Paper No. 8, mailed 8/9/01 and reiterated below.**

Del Tito et al teach the construction and use of a plasmid, pRI952, which comprises an array of two tRNA genes (argU and ileX) encoding tRNAs specific for the rarely used codons AGG/AGA and AUA, respectively (page 7087, paragraph 2; Tables I and II). The authors teach

that pRI952 was constructed by insertion of a PCR-amplified DNA comprising the gene for ileX flanked by HindIII restriction sites into pDC592, a pACYC184 derivative (i.e. low copy number) already possessing the argU gene (page 7087, column 2, paragraph 2). Del Tito et al teach that coexpression of the two tRNA genes along with the gene encoding the heterologous polypeptide Mup^r IRS results in increased levels of active protein as compared to a control in which no additional tRNA genes are expressed or as compared to cells comprising a plasmid only expressing the ileX gene (Table II). Del Tito et al teach that "..problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page 7087, column 1, paragraph 2). The authors conclude that the coexpression of minor tRNAs such as ileX or argU can be utilized to overcome translational stresses due to the presence of rarely used codons within the coding sequence for a gene of interest (page 7091, column 1, paragraph 3). Del Tito et al teach the purification by reverse phase HPLC of another heterologous polypeptide (i.e. the B/LeeHA antigen) produced by their system for compensating for the presence of rare codons in the coding sequence for the desired polypeptide (page 7088, column 1, paragraphs 3-4).

Del Tito et al do not explicitly teach the use of a vector comprising an array of 3 or more tRNAs corresponding to rarely used codons for overexpression of a heterologous gene comprising rarely used codons. Del Tito et al do not explicitly teach the use of ileY, proL, leuW.

Makoff et al teach that the expression of the tetanus toxin fragment C in E.coli is limited by its high demand for rare tRNA molecules (page 10193, paragraph 2). Makoff et al teach that

fragment C comprises several different rare codons specifying different amino acids (i.e. Leu, Ile, Ser, Pro, Arg and Gly) which are fairly evenly spread out through the coding sequence (Table 2; page 10196, paragraph 2). Makoff et al teach that replacement of almost the entire coding sequence with synthetic sequence which lacks the rarely used codons results in an approximate 4-fold increase in expression of the desired heterologous polypeptide (page 10199, paragraph 2). Makoff et al teach that fragment C from tetanus toxin shows considerable promise as a subunit vaccine against tetanus (page 10193, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by Del Tito comprising argU and ileX for increasing the expression of a desired heterologous polypeptide whose gene comprises rarely used codons by introducing additional tRNA genes corresponding to rarely used codons other than AGA, AGG or AUA in order to express the tetanus fragment C subunit in E.coli as taught by Makoff et al because Del Tito et al teach that it is within the skill of the art to express tRNA genes corresponding to different rarely used codons from the same vector in order to compensate for the presence of the rarely used codons in a gene encoding a desired heterologous polypeptide, because Makoff et al teach it is within the skill of the art to increase the expression of fragment C in E.coli by compensating for the presence of a number of different rarely used codons in the gene encoding fragment C and because tRNA genes corresponding to the rarely used codons in the gene encoding tetanus toxin fragment C are and were known in the art. One would have been motivated to do so in order to receive the expected benefit of expressing increased levels of

fragment C from the native gene encoding fragment C without having to synthetically construct a gene encoding fragment C which lacks the rarely used codons. Based upon the combined teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing a vector made from the combined teachings above comprising 3 or more tRNA genes corresponding to the rare codons present in the coding sequence for fragment C, as taught by Makoff et al, to overexpress fragment C from its native gene in E.coli.

With regard to the different tRNA genes recited in the rejected claims (e.g. ileY, proL or leuW), it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate any tRNA gene known in the art into the vector made from the combined teachings above in order to provide the necessary tRNAs to compensate, as taught by Del Tito et al, for the presence of the rarely used codons present in the fragment C gene, as taught by Makoff et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing such tRNA genes in the expression system made from the combined teachings above to increase the expression of fragment C in E.coli.

Claims 6-9, 19, 21 and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U) in view of Makoff et al (V) as applied to claims 1-5, 10-17, 22-23 and 26-38 above, and further in view of the 1997 Novagen catalog (pages 42-44) (W). **This rejection is maintained for reasons of record in Paper No. 8, mailed 8/9/01 and reiterated below.**

The teachings of Del Tito et al and Makoff et al are described above and applied as before, except:

Del Tito et al teaches that the expression of tRNA genes has been shown to be deleterious to the host cell and that for this reason the ileX promoter was used to control expression of the ileX gene from low-copy number plasmids (page 7090, column 2, paragraph 3).

Neither reference teaches the use of a vector in which the expression of the tRNA genes is regulated by an IPTG inducible promoter, the use of a T7 RNA polymerase promoter or protease deficient cells.

The 1997 Novagen catalog (pages 42-44; Figure 1) describes a T7 RNA polymerase expression system for tight control over the expression of toxic genes in E.coli. The system features 1) the use of a λ lysogen (DE3) which comprises the gene for T7 RNA polymerase under control of an IPTG-inducible promoter, 2) a T7lac promoter which is also inducible upon addition of IPTG and (page 44) and 3) an E.coli strain which lacks functional genes for the Lon and OmpT proteases (page 43, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to clone the tRNA genes for tRNAs corresponding to rarely used codons used in the methods made from the combined teachings above into one of the pET vectors/expression systems described in the 1997 Novagen catalog because Del Tito et al teach that it is within the skill of the art to compensate for the presence of rarely used codons in the gene for a polypeptide of interest by expressing the corresponding tRNA genes from a vector in E.coli, because Del Tito

et al also teach that the expression of tRNA genes in E.coli can have negative effects on the host cells and because the T7 RNA polymerase-based system described in the Novagen catalog for tightly controlled expression of target, toxic genes in E.coli was well known and widely used within the art for the expression of toxic genes in E.coli. One would have been motivated to do so in order to avoid any potential toxic effects associated with the expression of the tRNA genes in E.coli. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing the pET expression system for the controlled expression of tRNA genes in E.coli for the purposes of expression desired polypeptides whose genes comprise a number of different, rarely used codons.

Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U) in view of Makoff et al (V) and the 1997 Novagen catalog (W) as applied to claims 1-17, 19 and 21-38 above, and further in view of Wnendt (X). **This rejection is maintained for reasons of record in Paper No. 8, mailed 8/9/01 and reiterated below.**

The teachings of Del Tito et al, Makoff et al and the 1997 Novagen catalog are described above and applied as before, except:

The cited references do not teach the use of endA$^-$ E.coli strains.

Wnendt teaches that the use of endA$^-$ strains allows for great and higher quality yields of plasmid DNAs from bacterial cells (page 270, column 1, paragraph 1).

It would have been obvious to one of ordinary skill in the art to introduce an endA mutation into the strain of E.coli used in the method made from the combined teachings above to express heterologous polypeptides whose genes comprise different rarely-used codons because Wnendt teaches that the lack of EndA nuclease activity results in higher quantity and quality of plasmids isolated from E.coli strains bearing an endA mutation. One would have been motivated to do so in order to increase the yield and quality of plasmids recovered from the host cells during cloning of the vectors comprising the tRNA genes corresponding to the rarely used codons present in the gene encoding a desired polypeptide. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing an endA$^-$ strain of E.coli in the methods made from the combined teachings above for expression of a gene encoding a desired polypeptide comprising rarely used codons.

Claims 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U). **This rejection is maintained for reasons of record in Paper No. 8, mailed 8/9/01 and reiterated below.**

Del Tito et al teach the construction and use of a plasmid, pRI952, which comprises an array of two tRNA genes (argU and ileX) encoding tRNAs specific for the rarely used codons AGG/AGA and AUA, respectively (page 7087, paragraph 2; Tables I and II). Del Tito et al teach that coexpression of the two tRNA genes along with the gene encoding the heterologous polypeptide Mup^r IRS results in increased levels of active protein as compared to a control in

which no additional tRNA genes are expressed or as compared to cells comprising a plasmid only expressing the ileX gene (Table II). Del Tito et al teach that "..problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page 7087, column 1, paragraph 2). The authors conclude that the coexpression of minor tRNAs such as ileX or argU can be utilized to overcome translational stresses due to the presence of rarely used codons within the coding sequence for a gene of interest (page 7091, column 1, paragraph 3).

Del Tito et al do not explicitly teach the use of any vector nucleic acid comprising two tRNA genes corresponding to rarely used codons other than a vector comprising argU and ileX. Del Tito et al do not teach the use of ileY, proL , leuW or a tRNA corresponding to rarely used glycine codons.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector construct taught by Del Tito et al for compensating for the presence of rarely used codons present in the gene encoding a polypeptide of interest by interchanging different tRNA genes corresponding to other rarely used codons (i.e. other than AGG/AGA or AUA) because Del Tito et al teach that it is within the skill of the art to carefully scrutinize the coding sequence for a desired polypeptide, identify rarely used codons and compensate for the presence of such rarely used codons by supplying in trans the tRNA corresponding to the identified rarely used codons from a vector expressing different tRNA genes, and because such rarely used codons and the genes for their corresponding tRNAs are and were known in the art.

One would have been motivated to do so in order to meet the particular rare-codon requirements of a gene encoding a desired polypeptide and thus receive the expected benefit of increasing its expression in E.coli, as taught by Del Tito et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing any tRNA gene known in the art (i.e. ileY, proL, leuW, etc.) in the vector taught by Del Tito et al to increase the production of a desired polypeptide in E.coli whose gene comprises different rarely used codons.

Response to Arguments

Applicant's arguments filed 2/9/01 have been fully considered but they are not persuasive.

Applicant's response essentially argues: 1) the Del Tito et al reference teaches away from the claimed invention, 2) the combination of references (i.e. Del Tito et al and Makoff et al) do not provide the claimed invention, 3) the further references (i.e. Wnendt, Novagen catalog) do not make up for the shortcomings of the two primary references with regard to the claimed invention, and 4) the invention has met with significant commercial success.

With regard to the assertion that the Del Tito et al reference "teaches away" from the claimed invention, applicant's assertion is based upon one example (i.e. one polypeptide) wherein the combination of the tRNA genes ileX and argU was not as effective as ileX alone. As noted above, Del Tito et al provide another example (i.e. Mup^r IRS) wherein the nucleic acid encoding the protein comprises a different composition with regard to rarely used codons and wherein the combination of ileX and argU genes was more effective than ileX alone (Table 2 of Del Tito et

al). The argument presented in the response that the lack of a control wherein the effect of argU alone on expression of Mup^r IRS somehow affects the validity of the Mup^r IRS experiment is irrelevant in that 1) Del Tito et al demonstrate that the combination of ileX and argU is better than ileX alone (i.e. the combination works), and 2) there is no reason to expect that the requirements for argU in Mup^r IRS are so stringent that argU alone might do better than the combination of argU and ileX (e.g. a higher percentage of rare, arginine-specific codons in Mup^r IRS as compared to flu B/LeeHA). As noted above, Del Tito et al teach that "..problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page 7087, column 1, paragraph 2). Based upon the totality of the teachings presented by Del Tito et al, one cannot conclude that the reference actually teaches away from the claimed invention. One of skill in the art, upon reading the teachings provided by Del Tito et al would reasonably conclude that one could determine the rare codon usage for a given gene to be expressed in E.coli, design an appropriate vector/host system to provide the tRNA genes corresponding to the rarely used codons, and use that system to more efficiently produce a protein encoded by a nucleic acid having rarely used codons than in the absence of such a vector/host system. There is no reason to conclude, based upon the teachings of Del Tito et al, that one could not incorporate additional and/or different known tRNA genes and use such a vector/host system with a reasonable expectation of success.

With regard to the assertion that the combination of the two primary references does not teach or suggest the entire invention, the assertion is not accurate. The combination of the two

references does in fact provide the claimed invention. The differences between the Del Tito et al reference and the claimed invention are essentially two-fold: 1) the claimed invention encompasses embodiments wherein three or more tRNA genes are arranged in an array whereas Del Tito et al teach embodiments of only two tRNA genes on a vector, and/or 2) the instant claims encompass tRNA genes not taught by Del Tito. Del Tito et al teach that "..problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page 7087, column 1, paragraph 2). One of skill in the art would necessarily conclude from reading the entirety of the Del Tito et al teachings that the phrase cited above would include the use of different combinations of tRNA genes known in the art and in numbers of such genes as are needed to complement for the different rarely used codons present in a desired gene. The Makoff et al reference provides a desired polypeptide whose corresponding gene comprises a number of different rarely-used codons for which corresponding tRNA genes are and were known in the art. The rarely used codons described by Makoff et al (see Table 2; e.g. CUA, AUA, CCC, CGA, CGG, AGA, AGG, GGA), and which were corrected in the coding sequence by Makoff et al to improve expression of the desired polypeptide, have corresponding tRNAs for which the genes were known at the time of applicant's invention (e.g. leuW). As noted above, one of ordinary skill in the art would have been motivated to produce the polypeptide described by Makoff et al in E.coli with the methods taught by Del Tito et al in order to receive the expected benefit of expressing increased levels of fragment C in E.coli from the native gene encoding fragment C without having to

synthetically construct a gene encoding fragment C which lacks the rarely used codons. Based upon the combined teachings of Del Tito et al (i.e. that one can compensate for the presence of rarely used codons in a gene encoding a desired protein by providing correspond tRNAs in the host cell) and Makoff et al (fragment C can be more efficiently expressed when most of the rarely used codons are compensated for), there would have been a reasonable expectation of success in using the methods taught by Del Tito et al to express the polypeptide taught by Makoff et al in E.coli.

With regard to the assertion that the remaining references (Wnendt and the Novagen catalog) do not overcome the deficiencies of the Del Tito et al and Makoff et al references, 1) the Del Tito et al and Makoff et al references provide the basic invention and are not deficient, and 2) the remaining references were utilized to provide specific limitations to the basic invention (i.e. use of an endA- host strain and/or use of an IPTG-inducible T7 expression system).

With regard to the Rule 132 Declaration provided by Mary Buchanan, the declaration has been considered but is not deemed persuasive with regard to obviousness of the claimed invention. There is no background provided against which to judge the degree of success for the claimed invention. Are there any other host strains on the market today for expression of polypeptides comprising rarely used codons? How do the sales figures for the embodiments described by Ms. Buchanan compare to such strains? How do the sales figures compare to other expression hosts available on the market? Gross sales figures alone do not show commercial success absent any evidence to market share, the time period during which the product was sold,

or as to what sales would normally be expected in the market (Ex parte, Standish, 10 USPQ2d 1454; see MPEP 716.03(b)). The data provided thus far is not indicative of such a degree of commercial success that the claimed invention is not obvious. Some relevant background figure needs to be provided against which the figures provided in the declaration can be compared.

Secondly, the strain/vector combinations described in the specification are all drawn towards embodiments wherein the combination of tRNA genes in an array are either argU-ileY-leuW or argU-proL. Even if one were to grant that the sales figures provided by the declaration indicate commercial success for these embodiments, it is not clear that such a demand would be present for other claimed embodiments (e.g. ileY-leuW) wherein the tRNA gene combinations may not correspond to a significant number of eukaryotic genes comprising combinations of those rarely used codons.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The

examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application, or relating to attachments to this office action, should be directed to the Patent Analyst Zeta Adams, whose telephone number is (703) 305-3291.

GLL

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER

May 3, 2001